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TITLE: Identification of peptides that facilitate uptake and cytoplasmic and/or nuclear transport of proteins, DNA and viruses

PUBLICATION-DATE: November 27, 2003

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US-CL-CURRENT: 435/7.1; 435/194, 435/226, 530/328

CLAIMS:

We claim:

1. A peptide having an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

2. A peptide-cargo complex comprising a peptide and a cargo wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

3. The peptide-cargo complex of claim 2, wherein the cargo is an apoptotic protein selected from the group consisting of p53, caspase-3, HSV thymidine kinase, smac and an antimicrobial peptide.

4. A method for identifying peptides capable of cellular internalization of cargo linked thereto, said method comprising: incubating a target cell with a peptide display library;

isolating internalized peptides presented by said peptide display library from said target cells and identifying said peptides; synthesizing said peptides; linking said peptides to cargo to form a peptide-cargo complex; incubating said peptide-cargo complex with a target cell; and determining the ability of said peptide to facilitate the cellular internalization of said cargo into said target cell.

5. An expression cassette comprising a DNA encoding a fusion protein comprising a leader sequence, a protein of interest and an internalizing peptide having an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

6. A method for inducing synovial cell death comprising administering a peptide-cargo complex to said synovial cell, wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

7. A method for inducing apoptosis in a tumor cell comprising administering a peptide-cargo complex to said tumor cell, wherein the peptide has the amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

8. A method for reducing white blood cells in arthritic joints comprising administering a peptide-cargo complex to said white blood cells, wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

9. A method for inhibiting apoptosis in an islet cell comprising administering a peptide-cargo complex to said islet cell, wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

10. A method for delivering anti-oxidant and anti-inflammatory agents to lung epithelial cells comprising administering a peptide-cargo complex to said lung epithelial cells, wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

11. The method of claim 5, 6, 7, 8, or 9 wherein the apoptotic protein is selected from the group consisting of p53, caspase-3, HSV thymidine kinase, smac and an antimicrobial peptide.

12. A method of internalization into a peptide-cargo complex into a cell, comprising administering to said cell an amount of said peptide-cargo complex and an agent which

facilitates internalization.

13. A method for internalizing a GST-fusion protein into a cell comprising administering to said cell a peptide-cargo complex and a GST fusion protein.

14. A kit for internalizing a GST-fusion protein into a cell comprising a peptide-cargo complex.

15. An immunogen comprising a peptide-cargo complex wherein said peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO: 85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

16. A method for eliciting an immune response in a subject comprising administering to a target cell of said subject an immunogen comprising a peptide-cargo complex wherein said peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG (SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

17. A peptide selected from the group consisting of: (i) a peptide having an amino acid sequence comprising interations of histidine residues, wherein said peptide comprises approximately 4 to 18 histidine residues; (ii) a peptide having an amino acid sequence comprising iterations of histidine residues interspersed with lysine, arginine and or orinthine residues wherein said peptide comprises approximately 4 to 18 residues; and (iii) a peptide having an amino acid sequence comprising iterations of orinithine residues wherein said peptide comprisies approximately 4 to 18 orinithine residues.

18. A peptide-cargo complex comprising the peptide of claim 17.

19. The peptide-cargo complex of claim 18, wherein the cargo is an apoptotic protein selected from the group consisting of p53, caspase-3, HSV thymidine kinase and an antimicrobial peptide.

20. An expression cassette comprising a DNA encoding a fusion protein comprising a leader sequence, a protein of interest and the peptide of claim 17.

21. A transfer vector comprising the expression cassette of claim 20.

22. A method for inducing synovial cell death comprising administering a peptide-cargo complex to said synovial cell, wherein the peptide is the peptide of claim 17.

23. A method for inducing apoptosis in a tumor cell comprising administering a peptide-cargo complex to said tumor cell, wherein the peptide is the peptide of claim 17.

24. A method for reducing white blood cells in arthritic joints comprising administering a peptide-cargo complex to said white blood cells, wherein the peptide is the peptide of claim 17.

25. A method for inhibiting apoptosis in an islet cell comprising administering a peptide-cargo complex to said islet cell, wherein the peptide is the peptide of claim 17.

26. A method for delivering anti-oxidant and anti-inflammatory agents to lung epithelial cells comprising administering a peptide-cargo complex to said lung epithelial cells, wherein the peptide is the peptide of claim 17.

27. The method of claim 23 wherein the apoptotic protein is selected from the group consisting of p53, caspase3, HSV thymidine kinase, smac and an antimicrobial peptide.

28. A kit for internalizing a GST-fusion protein into a cell comprising a peptide-cargo complex wherein the peptide is the peptide of claim 17.

29. An immunogen comprising a peptide-cargo complex wherein said peptide is the peptide of claim 17.

30. A method for eliciting an immune response in a subject comprising administering to a target cell of said subject an immunogen comprising a peptide-cargo complex wherein said peptide is the peptide of claim 1.

31. The method of claim 23 further comprising administering dentritic cells to said tumor cell.

32. The method of claim 23 further comprising administering rTRAIL to said tumor cells.

33. The method of claim 23 further comprising administering a DNA topoisomerase inhibitor to said tumor cells.

34. The method of claim 33 wherein said topoisomerase inhibitor is etoposide.

35. A peptide-cargo complex wherein said cargo is a smac peptide, smac functional variant, smac mutant peptide or smac peptiomimetic wherein said cargo is capable of inducing apoptosis

Terms	Documents
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L2: Entry 2 of 2 File: PGPB Jun 5, 2003

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TITLE: Identification of peptides that facilitate uptake and cytoplasmic and/or nuclear transport of proteins, DNA and viruses

PUBLICATION-DATE: June 5, 2003

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CLAIMS:

We claim:

1. A peptide having an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DP ARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

2. The peptide of claim 1 wherein said peptide facilitates cellular internalization of a cargo linked thereto.

3. The peptide of claim 2 wherein the peptide has the amino acid sequence TLPSPLALLTVH (SEQ ID NO:59).

4. The peptide of claim 2 wherein the peptide has the amino acid sequence SVSVGMKPSPRP (SEQ ID NO:86).

5. The peptide of claim 1 wherein the peptide provides for nuclear translocation in a target cell.

6. A peptide-cargo complex comprising a peptide and a cargo wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR

(SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

7. The peptide-cargo complex of claim 6 wherein the cargo is selected from the group consisting of a polynucleotide, a polypeptide, a small molecule, a virus, a modified virus, a viral vector, and a plasmid.

8. The peptide-cargo complex of claim 6 wherein the cargo is a virus selected from the group consisting of adenovirus, adeno-associated virus, herpes simplex virus, and retrovirus.

9. The peptide-cargo complex of claim 6 wherein the cargo is selected from the group consisting of therapeutic proteins, suicide proteins, tumor suppressor proteins, transcription factors, kinase inhibitors, kinases, cell cycle regulatory proteins, apoptotic proteins, anti-apoptotic proteins, viral antigens, cellular antigens, differentiation factors, immortalization factors, toxins, antibodies and inhibitors of NF-.kappa.B.

10. The peptide-cargo complex of claim 6 wherein the peptide facilitates cellular internalization of cargo linked thereto.

11. The peptide-cargo complex of claim 6 wherein the peptide provides for nuclear translocation of said peptide-cargo complex in a target cell.

12. The peptide-cargo complex of claim 6 wherein the peptide is biotinylated and the cargo is avidin labeled.

13. The peptide-cargo complex of claim 9, wherein the cargo is an apoptotic protein selected from the group consisting of p53, caspase-3, HSV thymidine kinase and an antimicrobial peptide.

14. The peptide-cargo complex of claim 6 wherein the cargo is glutathione.

15. The peptide-cargo complex of claim 6 wherein the peptide has the amino acid sequence TLPSPLALLTVH (SEQ ID NO:59).

16. The peptide-cargo complex of claim 6 wherein the peptide has the amino acid sequence SVSVGMKPSPRP (SEQ ID NO:86).

17. The peptide-cargo complex of claim 6 wherein the peptide is biotinylated and the cargo is avidin-labeled.

18. An expression cassette comprising a DNA encoding a fusion protein comprising a leader sequence, a protein of interest and an internalizing peptide having an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

19. The expression cassette of claim 18 further comprising expression control sequences operatively linked to said DNA.

20. A transfer vector comprising the expression cassette of claim 19.

21. The expression cassette of claim 18, wherein said leader sequences are selected from the group consisting of II-1ra, PTH, VP-22 and related sequences.

22. The expression cassette of claim 18 wherein the protein of interest is selected from the group consisting of apoptotic proteins, anti-apoptotic proteins, cell cycle regulatory proteins, transcription factors, suicide gene products, viral or tumor antigens, and cell proliferation factors.

23. The expression cassette of claim 18, wherein the encoded fusion protein comprises an amino acid sequence which facilitates removal of leader sequences therefrom and wherein said leaderless fusion protein comprises an internalizing peptide and a protein of interest.

24. The expression cassette of claim 18 wherein said fusion protein encoded thereby is produced and secreted from a cell and subsequently internalized into surrounding cells.

25. A method for inducing synovial cell death comprising administering a peptide-cargo complex to said synovial cell, wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

26. A method for inducing apoptosis in a tumor cell comprising administering a peptide-cargo complex to said tumor cell, wherein the peptide has the amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

27. A method for reducing white blood cells in arthritic joints comprising administering a peptide-cargo complex to said white blood cells, wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

28. A method for inhibiting apoptosis in an islet cell comprising administering a peptide-cargo complex to said islet cell, wherein the peptide has an amino acid sequence selected from the group consisting of KRIIQRILSRNS (SEQ ID NO: 1), KRIHPRLTRSIR (SEQ ID NO:2), PPRLRKRRQLNM (SEQ ID NO:3), PIRRRKKLRRLK (SEQ ID NO:4), RRQRRTSKLMKR(SEQ ID NO:5), MHKRPTTPSRKM (SEQ ID NO:6), RQRSRRRPLNIR (SEQ ID NO:7), RIRMIQNLIKKT (SEQ ID NO:8), SRRKRQRSNMRI (SEQ ID NO:9), QRIRKSKISRTL (SEQ ID NO:10), PSKRLLHNNLRR (SEQ ID NO: 11), HRHIRRQSLIML (SEQ ID NO: 12), PQNRLQIRRHSK (SEQ ID NO: 13), PPHNRIQRRLNM (SEQ ID NO:14), SMLKRNHSTSNR (SEQ ID NO: 15), GSRHPSLIIPRQ (SEQ ID NO: 16), SPMQKTMNLPPM (SEQ ID NO:17), NKRILIRIMTRP (SEQ ID NO:18), HGWZIHGLLHRA (SEQ ID NO:25), AVPAKKRZKSV (SEQ ID NO:26), PNTRVRPDVSF (SEQ ID NO:27), LTRNYEAWVPTP(SEQ ID NO:28), SAETVESCLAKSH (SEQ ID NO:29), YSHIATLPFTPT (SEQ ID NO:30), SYIQRTPSTTLP (SEQ ID NO:31), AVPAENALNNPF (SEQ ID NO:32), SFHQFARATLAS(SEQ ID NO:33), QSPTDFTFPNPL (SEQ ID NO:34), HFAAWGGWSLVH (SEQ ID NO:35), HIQLSPFSQSWR (SEQ ID NO:36), LTMPSDLQPVLW (SEQ ID NO:37), FQPYDHPAEVSY (SEQ ID NO:38), FDPFFWKYSPRD (SEQ ID NO:39), FAPWDTASFMLG (SEQ ID NO:40), FTYKNFFWLPEL (SEQ ID NO:41), SATGAPWKMWVR (SEQ ID NO:42), SLGWMLPFSPPF (SEQ ID NO:43), SHAFTWPTYLQL (SEQ ID NO:44), SHNWLPLWPLRP (SEQ ID NO:45), SWLPYPWHVPSS (SEQ ID NO:46), SWWTPWHVHSES (SEQ ID NO:47), SWAQHLSLPPVL (SEQ ID NO:48), SSSIFPPWLSFF (SEQ ID NO:49), LNVPPSWFLSQR(SEQ ID NO:50), LDITPFLSLTLP (SEQ ID NO:51), LPHPVLHMGPLR (SEQ ID NO:52), VSKQPYYMWNGN (SEQ ID NO:53), NYTTYKSHFQDR (SEQ ID NO:54), AIPNNQLGFPFK (SEQ ID NO:55), NIENSTLATPLS (SEQ ID NO:56), YPYDANHTRSPT (SEQ ID NO:57), DPATNPGPHFPR (SEQ ID NO:58), TLPSPLALLTVH (SEQ ID NO:59), HPGSPFPPEHRP (SEQ ID NO:60), TSHTDAPPARSP (SEQ ID NO:61), MTPSSLSTLPWP (SEQ ID NO:62), VLGQSGYLMPMR (SEQ ID NO:63), QPIIITSPYLPS (SEQ ID NO:64), TPKTMTQTYDFS (SEQ ID NO:65), NSGTMQSASRAT (SEQ ID NO:66), QAASRVENYMHR (SEQ ID NO:67), HQHKPPPLTNNW (SEQ ID NO:68), SNPWDSLLSVST (SED ID NO:69), KTIEAHPPYYAS (SEQ ID NO:70), EPDNWSLDFPRR(SEQ ID NO:71), HQHKPPPLTNNW (SEQ ID NO:72), GVVGKLGQRRTKKQRRQKK (SEQ ID NO:73), GRRTKKQRRQKKPPRYMILGLLALAAVCSAA (SEQ ID NO:74), GRRTKKQRRQKKPP (SEQ ID NO:75), MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

29. The method of claim 26, wherein the tumor cell is a prostate tumor cell.

30. A method for delivering anti-oxidant and anti-inflammatory agents to lung epithelial cells comprising administering a peptide-cargo complex to said lung epithelial cells, wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

31. The method of claim 25, 26, 27, 28, or 29 wherein the cargo is an apoptotic protein.

32. The method of claim 31 wherein the apoptotic protein is selected from the group consisting of p53, caspase-3, HSV thymidine kinase and an antimicrobial peptide.

33. The method of claim 32 wherein the antimicrobial peptide has an amino acid sequence selected from the group consisting of KLAKLAK (SEQ ID NO:22) and KLAKLAKKLAKLAK (SEQ ID NO:23).

34. The method of claim 30, wherein the anti-inflammatory agent is selected from the group consisting of NF-.kappa.B and CFTR peptides.

35. The method of claim 30, wherein the anti-oxidant is selected from the group consisting of superoxide dismutase (SOD) and manganese superoxide dismutase (MnSOD).

36. A method of internalization into a peptide-cargo complex into a cell, comprising administering to said cell an amount of said peptide-cargo complex and an agent which facilitates internalization.

37. The method of claim 53, wherein the agent is selected from the group consisting of dextran sulfate, heparan sulfate or protamine sulfate.

38. A method for internalizing a GST-fusion protein into a cell comprising administering to said cell a peptide-cargo complex and a GST fusion protein wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

39. The method of claim 38 wherein the cargo is glutathione.

40. A kit for internalizing a GST-fusion protein into a cell comprising a peptide-cargo complex wherein the peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

41. The kit according to claim 40 wherein the cargo is glutathione.

42. An immunogen comprising a peptide-cargo complex wherein said peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

43. The immunogen of claim 42 wherein the peptide has an amino acid sequence RRQRRTSKLMKR (SEQ ID NO:5).

44. The immunogen of claim 42 wherein the peptide has an amino acid sequence GVVGKLGQRRTKKQRRQKK (SEQ ID NO:73).

45. The immunogen of claim 42 wherein the cargo is selected from the group consisting of a polynucleotide, a polypeptide, a protein, a virus, a modified virus, a viral vector, and a plasmid.

46. The immunogen of claim 42 wherein the cargo is an antigen.

47. The immunogen of claim 42 wherein the cargo is an HIV protein selected from the group consisting of Gag, Pol, Env, Tat, Nef, Vpr, Vpv, Rev.

48. A method for eliciting an immune response in a subject comprising administering to a target cell of said subject an immunogen comprising a peptide-cargo complex wherein said peptide has an amino acid sequence selected from the group consisting of MYRPPAANVDPW (SEQ ID NO:76), SSPPPDLTTRTP (SEQ ID NO:77), ATTQSTPPAFHL (SEQ ID NO:78), SDLPHVSSYWRG(SEQ ID NO:79), TTTQFMEIRQSA (SEQ ID NO:80), GKTWKASDEDWT (SEQ ID NO:81), DPARILGRIFL (SEQ ID NO:82), YNLQPTTSARPT (SEQ ID NO:83), SLKTPTTSHLSQ (SEQ ID NO:84), TFDLRNNTHRNP (SEQ ID NO:85), SVSVGMKPSPRP (SEQ ID NO:86), RRQRR (SEQ ID NO:97), RRQRRQRR (SEQ ID NO:98), RRQRRQRRQRR (SEQ ID NO:99).

49. The method of claim 48 wherein the target cell is a mucosal cell.

50. The method of claim 49 wherein the mucosal cell is a cervical mucosal cell.

Previous Doc Next Doc Go to Doc#

L1 11 CFTR AND (HDJ2 OR HSC/HSP70)

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2 7 DUP REM L1 (4 DUPLICATES REMOVED)

=> d l2 1-7 ibib ab

L2 ANSWER 1 OF 7 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:530881 BIOSIS Full-text
DOCUMENT NUMBER: PREV200510324396
TITLE: Maturation and functional restoration of DeltaF508CFTR by its subdomains in cystic fibrosis airway cells.
AUTHOR(S): Sun, Fei [Reprint Author]; Condliff, Steven B.; Bertrand, Carol A.; Mi, Zhibao; Pilewski, Joseph M.; Robbins, Paul D.; Bridges, Robert J.; Frizzell, Raymond A.
CORPORATE SOURCE: Univ Pittsburgh, Pittsburgh, PA 15261 USA
SOURCE: FASEB Journal, (MAR 4 2005) Vol. 19, No. 4, Suppl. S, Part 1, pp. A574.
Meeting Info.: Experimental Biology 2005 Meeting/35th International Congress of Physiological Sciences. San Diego, CA, USA. March 31 -April 06, 2005. Amer Assoc Anatomists; Amer Assoc Immunologists; Amer Physiol Soc; Amer Soc Biochem & Mol Biol; Amer Soc Investigat Pathol; Amer Soc Nutr Sci; Amer Soc Pharmacol & Expt Therapeut; Int Union Physiol Sci.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Dec 2005
Last Updated on STN: 1 Dec 2005

AB Mutations in the cystic fibrosis transmembrane conductance regulator (**CFTR**) gene cause cystic fibrosis (CF), associated with a loss of cAMP-regulated anion conductance at epithelial cell apical membranes. The common folding mutant, DF508CFTR, is retained in the endoplasmic reticulum (ER) and is degraded by ubiquitin-proteasome pathways. DF508CFTR retention in the ER involves prolonged association with molecular chaperones. We show that expression of first nucleotide-binding domain plus the regulatory domain (RD) from DF508CFTR (DFRD) facilitates the biogenesis of mature, full-length DF508CFTR protein and elicits cAMP-stimulated anion transport in primary human bronchial epithelial cells isolated from homozygous DF508 CF patients (DF/DF cells). Fusion of DFRD with a protein tranduction domain evokes a dose-dependent, cAMP-stimulated anion efflux in DF/DF cells. The co-chaperone, **Hdj2**, selectively binds DF508CFTR. Expressionof DFRD produced a dose-dependent decrease in the DF508CFTR-**Hdj2** interaction and elicited a decrease in DF508CFTR protein aggregation. These data indicate that disruption of the interactions of **Hdj2** with DF508CFTR restores its maturation, trafficking and regulated anion channel activity. Protein transduction domain-mediated DFRD fragment delivery may provide a therapy for CF.

L2 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:203945 HCAPLUS Full-text
DOCUMENT NUMBER: 140:231208
TITLE: Polypeptides for increasing mutant **CFTR** channel activity
INVENTOR(S): Robbins, Paul D.; Frizzell, Raymond; Mi, Zhibao; Sun,

Fei
PATENT ASSIGNEE(S): University of Pittsburgh of the Commonwealth System of Higher Education, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004020596	A2	20040311	WO 2003-US327110	20030828
WO 2004020596	A3	20040902		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003272248	A1	20040319	AU 2003-272248	20030828
US 2004115770	A1	20040617	US 2003-650435	20030828
PRIORITY APPLN. INFO.:			US 2002-407461P P	20020830
			WO 2003-US27110 W	20030828

AB The present invention provides methods and compns. for enhancing channel activity to the mutant cystic fibrosis trans-membrane conductance regulator protein (**CFTR**). The compns. of the invention comprise polypeptides containing **CFTR** sub-domains that are designed to mimic the folding defect of the full length mutant **CFTR** proteins, resulting in competitive binding to cytoplasmic chaperones such as Hsc/Hsp70 and **Hdj2**. The methods of the invention comprise transduction, or recombinant expression, of **CFTR** polypeptides in a cell expressing mutant **CFTR**. The presence of the **CFTR** polypeptide results in a dominant effect whereby the **CFTR** polypeptide competes with the endogenously expressed mutant **CFTR** for binding to cytoplasmic chaperones such as Hsc/Hsp70 and **Hdj2** . Mutant **CFTR** proteins include, but are not limited to, ΔF508 **CFTR**. The present invention is based on the discovery that reduced binding of cytoplasmic chaperones to the endogenous ΔF508 **CFTR**, mediated by the presence of **CFTR** polypeptides, results in restoration of plasma membrane localization and channel activity. The methods and compns. of the invention can be used to restore channel activity in cystic fibrosis subjects carrying genetic defects in the **CFTR** gene, such as for example, ΔF508 **CFTR**.

L2 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2005025204 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15611333
TITLE: A foldable **CFTR**{Delta}F508 biogenic intermediate accumulates upon inhibition of the Hsc70-CHIP E3 ubiquitin ligase.
AUTHOR: Younger J Michael; Ren Hong-Yu; Chen Liling; Fan Chun-Yang; Fields Andrea; Patterson Cam; Cyr Douglas M
CORPORATE SOURCE: Department of Cell and Developmental Biology, School of Medicine, University of North Carolina, Chapel Hill, NC 27599, USA.
SOURCE: The Journal of cell biology, (2004 Dec 20) Vol. 167, No. 6,

pp. 1075-85.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 19 Jan 2005
Last Updated on STN: 9 Feb 2005
Entered Medline: 8 Feb 2005

AB CFTRDeltaF508 exhibits a correctable protein-folding defect that leads to its misfolding and premature degradation, which is the cause of cystic fibrosis (CF). Herein we report on the characterization of the CFTRDeltaF508 biogenic intermediate that is selected for proteasomal degradation and identification of cellular components that polyubiquitinate CFTRDeltaF508. Nonubiquitinated CFTRDeltaF508 accumulates in a kinetically trapped, but folding competent conformation, that is maintained in a soluble state by cytosolic Hsc70. Ubiquitination of Hsc70-bound CFTRDeltaF508 requires CHIP, a U box containing cytosolic cochaperone. CHIP is demonstrated to function as a scaffold that nucleates the formation of a multisubunit E3 ubiquitin ligase whose reconstituted activity toward **CFTR** is dependent upon **Hdj2**, Hsc70, and the E2 UbcH5a. Inactivation of the Hsc70-CHIP E3 leads CFTRDeltaF508 to accumulate in a nonaggregated state, which upon lowering of cell growth temperatures, can fold and reach the cell surface. Inhibition of CFTRDeltaF508 ubiquitination can increase its cell surface expression and may provide an approach to treat CF.

L2 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:8589 HCAPLUS Full-text
DOCUMENT NUMBER: 137:136496
TITLE: Hsp70 and its co-chaperones: key regulators of the intracellular fate of **CFTR**
AUTHOR(S): Meacham, Geoffrey Christopher
CORPORATE SOURCE: Univ. of Alabama, Birmingham, AL, USA
SOURCE: (2001) 196 pp. Avail.: UMI, Order No. DA3003386
From: Diss. Abstr. Int., B 2001, 62(2), 645
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L2 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:645844 HCAPLUS Full-text
DOCUMENT NUMBER: 133:217730
TITLE: Modulation of protein expression using carbocyclic aryl alkenoic acid derivatives, and treatment of disease modulated by undesired protein expression
INVENTOR(S): Zeitlin, Pamela L.; Brusilow, Saul
PATENT ASSIGNEE(S): Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000053174	A1	20000914	WO 2000-US6377	20000311

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-124297P P 19990312
OTHER SOURCE(S): MARPAT 133:217730

AB The invention generally relates to diseases or conditions modulated by undesired protein expression. In one aspect, the methods of the invention provide for administration to a mammal, particularly a human, of a therapeutically effective amount of a carbocyclic aryl compound capable of modulating that undesired protein expression. Assays for detecting compds. having desired therapeutic capacity are also provided.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2000131243 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10666020
TITLE: Sodium 4-phenylbutyrate downregulates Hsc70: implications for intracellular trafficking of DeltaF508-**CFTR**.
AUTHOR: Rubenstein R C; Zeitlin P L
CORPORATE SOURCE: Division of Pulmonary Medicine, Children's Hospital of Philadelphia and Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.. rrubenst@mail.med.upenn.edu
CONTRACT NUMBER: P01-HL-51811 (NHLBI)
SOURCE: American journal of physiology. Cell physiology, (2000 Feb) Vol. 278, No. 2, pp. C259-67.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 27 Apr 2000
Last Updated on STN: 27 Apr 2000
Entered Medline: 14 Apr 2000

AB The most common mutation of the cystic fibrosis transmembrane conductance regulator (**CFTR**), DeltaF508, is a trafficking mutant that has prolonged associations with molecular chaperones and is rapidly degraded, at least in part by the ubiquitin-proteasome system. Sodium 4-phenylbutyrate (4PBA) improves DeltaF508-**CFTR** trafficking and function in vitro in cystic fibrosis epithelial cells and in vivo. To further understand the mechanism of action of 4PBA, we tested the hypothesis that 4PBA modulates the targeting of DeltaF508-**CFTR** for ubiquitination and degradation by reducing the expression of Hsc70 in cystic fibrosis epithelial cells. IB3-1 cells (genotype DeltaF508/W1282X) that were treated with 0.05-5 mM 4PBA for 2 days in culture demonstrated a dose-dependent reduction in Hsc70 protein immunoreactivity and mRNA levels. Immunoprecipitation with Hsc70-specific antiserum demonstrated that Hsc70 and **CFTR** associated under control conditions and that treatment with 4PBA reduced these complexes. Levels of immunoreactive Hsp40, **Hdj2**, Hsp70, Hsp90, and calnexin were unaffected by 4PBA treatment. These data suggest that 4PBA may improve DeltaF508- **CFTR** trafficking by allowing a greater proportion of mutant **CFTR** to escape association with Hsc70.

L2 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:241434 HCAPLUS Full-text
DOCUMENT NUMBER: 131:41207
TITLE: The Hdj-2/Hsc70 chaperone pair facilitates early steps in **CFTR** biogenesis
AUTHOR(S): Meacham, Geoffrey C.; Lu, Zhen; King, Scott; Sorscher, Eric; Tousson, Albert; Cyr, Douglas M.
CORPORATE SOURCE: Department of Cell Biology, School of Medicine and Dentistry, University of Alabama Medical Center, Birmingham, AL, 35209, USA
SOURCE: EMBO Journal (1999), 18(6), 1492-1505
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cystic fibrosis transmembrane conductance regulator (**CFTR**) is a chloride ion channel constructed from two membrane-spanning domains (MSDs), two nucleotide-binding domains (NBD) and a regulatory (R) domain. The NBDs and R-domain are cytosolic and how they are assembled with the MSDs to achieve the native **CFTR** structure is not clear. Human DnaJ 2 (Hdj-2) is a co-chaperone of heat shock cognate 70 (Hsc70) which is localized to the cytosolic face of the ER. Whether Hdj-2 directs Hsc70 to facilitate the assembly of cytosolic regions on **CFTR** was investigated. We report that immature ER forms of **CFTR** and ΔF508 **CFTR** can be isolated in complexes with Hdj-2 and Hsc70. The ΔF508 mutation is localized in NBD1 and causes the **CFTR** to misfold. Levels of complex formation between ΔF508 **CFTR** and Hdj-2/Hsp70 were .apprx.2-fold higher than those with **CFTR**. The earliest stage at which Hdj-2/Hsc70 could bind **CFTR** translation intermediates coincided with the expression of NBD1 in the cytosol. Interestingly, complex formation between Hdj-2 and nascent **CFTR** was greatly reduced after expression of the R-domain. In expts. with purified components, Hdj-2 and Hsc70 acted synergistically to suppress NBD1 aggregation. Collectively, these data suggest that Hdj-2 and Hsc70 facilitate early steps in **CFTR** assembly. A putative step in the **CFTR** folding pathway catalyzed by Hdj-2/Hsc70 is the formation of an intramol. NBD1-R-domain complex. Whether this step is defective in the biogenesis of ΔF508 **CFTR** will be discussed.

REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 14:23:11 ON 27 APR 2006)

FILE 'MEDLINE, HCAPLUS, BIOSIS, BIOTECHDS' ENTERED AT 14:24:29 ON 27 APR 2006
L1 11 S CFTR AND (HDJ2 OR HSC/HSP70)
L2 7 DUP REM L1 (4 DUPLICATES REMOVED)

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	34.13	34.55
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.25	-2.25

STN INTERNATIONAL LOGOFF AT 14:34:06 ON 27 APR 2006

Hit List

First Hit Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 7 of 7 returned.

☐ 1. Document ID: US 20050074884 A1

Using default format because multiple data bases are involved.

L1: Entry 1 of 7 File: PGPB Apr 7, 2005

PGPUB-DOCUMENT-NUMBER: 20050074884
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050074884 A1

TITLE: Identification of peptides that facilitate uptake and cytoplasmic and /or nuclear transport of proteins, DNA and viruses

PUBLICATION-DATE: April 7, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Robbins, Paul D.	Mt. Lebanon	PA	US
Mi, Zhibao	Pittsburgh	PA	US
Frizzell, Raymond	Pittsburgh	PA	US
Glorioso, Joseph C.	Cheswick	PA	US
Gambotto, Andrea	Pittsburgh	PA	US

US-CL-CURRENT: 435/455; 435/456, 530/327, 530/328, 530/329, 530/330

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20040115770 A1

L1: Entry 2 of 7 File: PGPB Jun 17, 2004

PGPUB-DOCUMENT-NUMBER: 20040115770
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040115770 A1

TITLE: Polypeptides for increasing mutant CFTR channel activity

PUBLICATION-DATE: June 17, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Robbins, Paul D.	Mt. Lebanon	PA	US
Frizzell, Raymond	Pittsburgh	PA	US
Mi, Zhibao	Pittsburgh	PA	US
Sun, Fei	Warrendale	PA	US

US-CL-CURRENT: 435/69.1; 435/320.1, 435/325, 435/455, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 20030219826 A1

L1: Entry 3 of 7 File: PGPB Nov 27, 2003

PGPUB-DOCUMENT-NUMBER: 20030219826
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030219826 A1

TITLE: Identification of peptides that facilitate uptake and cytoplasmic and/or nuclear transport of proteins, DNA and viruses

PUBLICATION-DATE: November 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Robbins, Paul D.	Mt. Lebanon	PA	US
Mi, Zhibao	Pittsburgh	PA	US
Frizzell, Raymond	Pittsburgh	PA	US
Glorioso, Joseph C.	Cheswick	PA	US
Gambotto, Andrea	Pittsburgh	PA	US
Mai, Jeffrey C.	Pittsburgh	PA	US

US-CL-CURRENT: 435/7.1; 435/194, 435/226, 530/328

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 20030104622 A1

L1: Entry 4 of 7 File: PGPB Jun 5, 2003

PGPUB-DOCUMENT-NUMBER: 20030104622
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030104622 A1

TITLE: Identification of peptides that facilitate uptake and cytoplasmic and/or nuclear transport of proteins, DNA and viruses

PUBLICATION-DATE: June 5, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Robbins, Paul D.	Mt. Lebanon	PA	US
Mi, Zhibao	Pittsburgh	PA	US
Frizzell, Raymond	Pittsburgh	PA	US
Glorioso, Joseph C.	Cheswick	PA	US
Gambotto, Andrea	Pittsburgh	PA	US

US-CL-CURRENT: 435/455; 514/14, 514/15, 530/326, 530/327

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

---

☐ 5. Document ID: US 20020102265 A1

L1: Entry 5 of 7 File: PGPB Aug 1, 2002

PGPUB-DOCUMENT-NUMBER: 20020102265
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020102265 A1

TITLE: Isolation of a cell-specific internalizing peptide that infiltrates tumor tissue for targeted drug delivery

PUBLICATION-DATE: August 1, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Hong, Frank D.	Houston	TX	US
Clayman, Gary	Houston	TX	US

US-CL-CURRENT: 424/178.1; 424/1.49, 424/93.21, 435/320.1, 435/326, 435/69.1, 514/44, 530/389.1, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 6919425 B2

L1: Entry 6 of 7 File: USPT Jul 19, 2005

US-PAT-NO: 6919425
DOCUMENT-IDENTIFIER: US 6919425 B2

TITLE: Isolation of a cell-specific internalizing peptide that infiltrates tumor tissue for targeted drug delivery

DATE-ISSUED: July 19, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hong; Frank D.	Houston	TX		
Clayman; Gary	Houston	TX		

US-CL-CURRENT: 530/300

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 6881825 B1

L1: Entry 7 of 7 File: USPT Apr 19, 2005

US-PAT-NO: 6881825
DOCUMENT-IDENTIFIER: US 6881825 B1
**** See image for Certificate of Correction ****

TITLE: Identication of peptides that facilitate uptake and cytoplasmic and/or nuclear transport of proteins, DNA and virues

DATE-ISSUED: April 19, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Robbins; Paul D.	Mt. Lebanon	PA		
Mi; Zhibao	Pittsburgh	PA		
Frizzell; Raymond	Pittsburgh	PA		
Glorioso; Joseph C.	Cheswick	PA		
Gambotto; Andrea	Pittsburgh	PA		

US-CL-CURRENT: 530/327; 435/69.1, 435/69.7, 530/300, 530/326

Terms	Documents
CFTR and internalizing peptide	7